Updated Recommendations for Control of Surgical Site Infections

J. Wesley Alexander, MD, ScD, Joseph S. Solomkin, MD, and Michael J. Edwards, MD

Objective: The objective of this study is to provide updated guidelines for the prevention of surgical wound infections based upon review and interpretation of the current and past literature.

Background: The development and treatment of surgical wound infections has always been a limiting factor to the success of surgical treatment. Although continuous improvements have been made, surgical site infections continue to occur at an unacceptable rate, annually costing billions of dollars in economic loss caused by associated morbidity and mortality.

Methods: The Centers for Disease Control (CDC) provided extensive recommendations for the control of surgical infections in 1999. Review of the current literature with interpretation of the findings has been done to update the recommendations.

Results: New and sometimes conflicting studies indicate that coordination and application of techniques and procedures to decrease wound infections will be highly successful, even in patients with very high risks.

Conclusions: This review suggests that uniform adherence to the proposed guidelines for the prevention of surgical infections could reduce wound infections significantly; namely to a target of less than 0.5% in clean wounds, less than 1% in clean contaminated wounds and less than 2% in highly contaminated wounds and decrease related costs to less than one-half of the current amount.


The incidence of surgical site infections continues to be unacceptably high and most of these can be prevented. A review of the literature has been done with updated recommendations, which if applied routinely, could improve patient outcomes and save billions of dollars.

The direct economic costs of an SSI are considerable, usually being approximately twice the amount of in-patient costs for a patient without an SSI (SDC-1, SDC references at http://links.lww.com/SLA/A120). However, there are extreme variations in costs, ranging from less than $400/case for minor superficial infections noted after discharge to $63,135 for complex infections after insertion of joint prosthesis and $299,237 for mediastinitis after insertion of joint prosthesis and $299,237 for mediastinitis after open heart surgery (SDC-2–4). Home health care expenses after discharge may also be high – $620/patient in one study for infections after colon resection (SDC-5). In the 1990s, the median direct cost for hospitalization in infected patients was $7531 compared to $3844 for noninfected patients (SDC-6). The increase in costs for SSI ranged from $2671 for colon surgery to $11,001 for spinal surgery.

The overall costs of SSI to society can be staggering. In a study of hospital-associated infections in Massachusetts, the cost of such infections in 2006 was $223,000,000 to $275,000,000.1 A 1% incidence of SSI was projected to generate national costs of over $900,000,000 per year for in-hospital costs alone and a total of $1.6 billion in excess costs overall (SDC-7). Such figures may account for only 10% of overall costs when including indirect social costs such as time off work and loss of job. They also do not include potential costs for malpractice litigation and less tangible items such as loss of companionship. The economic cost is not the only cost. In an NNIS survey of 387,000 patients with nosocomial infections, an organ/space infection contributed to the death in 89% of the patients so afflicted (SDC-8). In another study involving 288,906 patients of which 11.9% had an SSI,2 in hospital mortality in infected, patients was 14.5% vs. 1.8% in noninfected patients.

REDUCTION IN CONTAMINATION (ASEPSIS)

OPERATING ROOM ENVIRONMENT

The CDC guidelines1 and regulations from various accrediting agencies are good resources for providing detailed guidance related to effective techniques for air handling, cleaning of environmental surfaces, sterilization techniques, activities of surgical team members, surgical attire, drapes, and asepsis. These should, in general, be regarded as recommendations which are set in stone.

Microbes in the air of the operating room can be an important source of pathogens for causing wound infections. High efficiency particulate air (HEPA) filters provide the best environment (SDC-9). Laminar flow systems may help, but show minimal protective effect on the incidence of surgical site infection compared to HEPA filtration (SDC-10). Limiting traffic and idle conversations in the operating room (OR) are essential to reducing airborne bacteria.

A major source of contamination of the operative wound is related to perforation of surgical gloves. In a recent study of 4147 surgical procedures, there was a higher likelihood of SSI in procedures in which gloves were perforated compared to procedures where they were not perforated (odds ratio, OR = 2.0) (SDC-11). The risk of infection with glove perforation was significantly greater in those procedures in which no antimicrobial prophylaxis was given. In an analysis of 655 surgical operations, perforations were found to occur in 31% (SDC-12). Double-indicator gloves made the intraoperative detection of perforations much easier. Using double gloving techniques, perforation of the outer glove was associated with less perforation of the inner glove (OR = 0.10) (SDC-13). Strike-through in operating gowns, particularly at the sleeve or abdominal area is also a potential source for contamination that is often neglected.

PREOPERATIVE BATHING WITH ANTISEPTIC AGENTS

Infections in clean surgery are most often caused by skin organisms and, consequently, there have been several approaches to decrease the number of bacteria colonizing the skin before patients come to the operating room. It is important, however, to note that organisms in sebaceous and other glands and hair follicles are not exposed to topical antiseptics. Bathing with hexachlorophene was shown to decrease wound infections in several studies before 1970 (SDC-14), but because chlorhexidine provided better long-term suppression of organisms than hexachlorophene, it soon became the preferred method.

From the University of Cincinnati College of Medicine, Department of Surgery, Cincinnati, Ohio.

Reprints: J. Wesley Alexander, MD, University of Cincinnati College of Medicine, Department of Surgery, 231 Albert Sabin Way, Cincinnati, OH 45267. E-mail: jwalexander@uc.edu.

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agent of choice. In a study of groin wounds in vascular surgery, the wound infection rate was decreased from 17.8% to 8% when patients showered 3 to 8 times preoperatively with chlorhexidine (SDC-15). Preoperative bathing with chlorhexidine has been shown to reduce the number of organisms at the incision site better than using povidone iodine or soap and water (SDC-16–17). Using a shower the evening before and the morning of an operation is more effective in colony reduction than a single shower either the night before or the morning of operation (SDC-18). Additional use of a cloth impregnated with chlorhexidine is more effective than simple showering. However, despite repeated demonstrations of a reduction in surface bacteria at the operative site using a chlorhexidine shower, recent meta-analyses have shown only a nonsignificant reduction in wound infections in large numbers of patients (SDC-19-22).

In a recent randomized trial examining MRSA detection/nasal decontamination/hexa-chlorophene showers, the significant reduction in infections seen was attributed to both treatments (SDC-23). It is well known that the nasal carriers are likely to have extranasal sites that are contaminated with the same strain and that carriers are at increased risk for endogenous S. aureus infections (SDC-24–25). The authors suggest that the use of chlorhexidine for simultaneous elimination of S. aureus from extranasal sites is needed to achieve the level of prophylaxis observed in this trial. Although this additional precaution might not lead to complete eradication of the organism, bacterial loads would probably be sufficiently reduced to prevent infection (SDC-26).

**Interpretation**

Preoperative bathing with chlorhexidine reduces pathogenic organisms on the skin but has a nonsignificant reduction in wound infections. The demonstration that a more substantial reduction of skin organisms using multiple showers or showers immediately before coming to the operating room suggests that timing might explain lower effectiveness in some of the reports. Cleansing with a cloth impregnated with chlorhexidine just before operation will provide additional removal of dirt and further reduction in skin bacteria.

**HAIR REMOVAL**

The dogma of preoperative shaving was challenged by a prospective randomized study in 1971 when it was documented that when hair was removed by a razor the wound infection rate was 5.6%, almost 10 times higher than when a depilatory was used (0.6%) or when no hair was removed (SDC-27). Two years later, a very large observational study of factors related to wound infections in 18,090 clean cases, revealed that patients who were shaved had an infection rate of 2.3% compared to 1.7% when hair was removed by clipper and 0.9% when no hair was removed (SDC-28). A prospective rando mized trial involving preoperative shaving vs. clipping was published in 1983, involving 1,013 patients. Including stitch abscesses, the overall rate of infection in patients prepped with a razor was 4.6% compared to 2.5% in those prepped with clippers. The best infection rate (1.8%) was found in the group prepped with a clipper on the morning of the operation. The benefit of clippers vs. the razor is supported by other studies in coronary artery bypass patients (OR = 3.25) (SDC-29). Neurosurgical patients are of particular interest because of the large amount of hair involved. Several studies have now shown that removal of hair by shaving compared to no shaving had no benefit on the incidence of postoperative infection (SDC-30–35). Two recent reviews using the Cochrane Database (SDC-36) and other methods of searching (SDC-37) have concluded that hair removal by clipper was superior to removal by a razor, but the infection rates were best when no hair was removed. There have been no prospective randomized trials, which compared clipping to the use of a depilatory cream.

**Interpretation**

It seems logical that the incidence of wound infection would increase when hair gets into a surgical wound. However, all of the evidence suggests that not removing hair is associated with the least infection. When it is deemed by the surgeon that hair should be removed, shaving should never be used. Clipping the hair with care to avoid skin damage seems to be the most satisfactory method. Most studies support hair removal done immediately before operation.

**SKIN DECONTAMINATION**

Alcohol has been used as a skin disinfectant for more than 150 years. It is clearly the most effective short-term antimicrobial but it is highly flammable. Furthermore, there is no persistence of the antimicrobial effect. A method using hand rubbing with 75% aqueous alcoholic solution compared to hand-scrubbing protocols with antiseptic preparation of 4% povidone iodine or 4% chlorhexidine gluconate show that there was no difference in the incidence of surgical site infection, but the hand-rubbing protocol was better tolerated (SDC-38). Alcohol hand gel preps were also well tolerated compared to soap and water handwashing (SDC-39). Conversely, several comparisons of chlorhexidine versus povidone-iodine have reported that chlorhexidine is more effective in reduction of skin bacteria and that chlorhexidine and alcohol provided even better reduction of bacteria. There have been several extensive reviews concerning antiseptic agents for preoperative skin preparation (SDC-40-42). The general conclusions of these reviews were that alcohol rubs were as effective as aqueous scrubs, chlorhexidine gluconate was more effective than povidone-iodine scrubs, and subsequent 2- to 3-minute scrubs were more effective than subsequent 30-second scrubs.

Combinations of alcohol and chlorhexidine or alcohol and an iodophor have been formulated to paint the area of the incision leading to a longer lasting barrier than prepping with aqueous materials. A recent study (SDC-43) showed that the overall rate of positive skin cultures was significantly lower in patients prepped with the chlorhexidine/alcohol product compared to an iodophor/alcohol product, and both of these were more effective in reducing positive cultures than a group prepped with aqueous povidone-iodine. In contrast, a very recent segmental observational study of 3209 operations showed a lower infection rate in patients prepped with iodine povidonex (4.8%) compared to a chlorhexidine/alcohol product (8.2%) (SDC-44). The only randomized trial found a greater than 40% reduction in total surgical-site infections among patients undergoing clean-contaminated surgery who had received a single chlorhexidine-alcohol scrub as compared with a povidone-iodine scrub (SDC-45).

**Interpretation**

Reduction of skin bacteria on hands of the surgical team with the use of various preparations is a surrogate marker for the occurrence of wound infections. Hand scrubs of 2 to 3 minutes using a chlorhexidine/alcohol based product will provide the greatest reduction in skin bacteria. The best reduction in microbes at the operative site seems to be with an iodine povidonex/alcohol or chlorhexidine/alcohol-based products.

**INCISE DRAPES**

The use of plastic adhesive incise drapes to prevent contamination of the wound from skin organisms has been used for at least 50 years. Reports of controlled studies have had mixed results, some showing some benefit (6, SDC-46–49) whereas others report no benefit (SDC50-54). A major part of these discrepancies is related to differences in the composition of the drapes themselves. The drapes available after 1985 are more pliable, have increased water vapor transmission and a more aggressive adhesive, which has an iodophor incorporated. Use of the older drapes without the iodophor has been associated with an increase in separation of the drape from the skin
edges at the incision. One study showed that if lifting at the edge of the skin occurs, the infection rate was 6-fold greater when compared to operations in which the incise drape did not lift.\(^6\) The studies before use of the new drape, in general, showed no benefit or an increase in infections when compared to no drape at all. Even when there was no difference in postoperative wound infection rates, the numbers of viable organisms on the surface of the skin at the completion of the operation was decreased by the use of the iodophor-containing drapes. Adhesiveness to the skin has been shown to improve with an initial alcohol or tincture of iodine solution prep of the skin (6, SDC-55). Conversely, use of a detergent increases the rate of lift. Adhesion to the skin has been most effective by preparation of the skin with alcohol followed by application of an alcohol-based iodophor (iodine povacrylex) and letting this dry thoroughly before application of the incise drape (SDC-55). Pressure should be applied to activate the pressure-sensitive glue. This type of drape application is also cost-effective when compared to skin preparation with povidone iodine alone (6, SDC-55).

A variant of this concept, application of a cyanoacrylate based “microbial sealant” to the operative site to trap microbes on the skin, has recently been introduced (SDC-56). This product has been shown to reduce wound colonization (SDC-57), but its ability to reduce infection needs further study before general recommendation.

**Interpretation**

The use of an adhesive antimicrobial incise drape may or may not decrease the incidence of wound infection, depending upon composition of the drape, preparation of the skin and adherence to the wound edges. Technique is important. With proper application of the incise drape to prevent lifting from the skin edge, contamination of the wound with skin organisms is not possible. A cyanoacrylate based skin sealant has been marketed recently, but requires further investigation.

**REDUCTION IN CONSEQUENCES OF CONTAMINATION (ANTISEPSIS) SUTURES**

The first study showing the importance of suture composition was reported in 1852 when sutures made out of silver were used for the successful repair of vesicovaginal fistulas, which had not been possible using silk (SDC-58).

In 1957, an experimental study showed that a silk suture placed in the subcutaneous tissues of humans could enhance the development of infection as much as 10,000-fold.\(^7\) A study 10 years later compared several types of suture material for potentiating wound infection in an experimental animal model (SDC-59). Linear polyethylene withstanded contamination the best and monofilament suture materials withstood contamination considerably better than braided or twisted configurations of the same material. There was no significant difference in the incidence of infection when comparing braided waxed silk, braided nylon, or twisted surgical cotton. Those findings were supported subsequently in a canine model using a similar technique (SDC-60). A more recent study (SDC-61) examined 16 types of suture for their resistance to both Gram-positive and Gram-negative infections using a mouse model. Synthetic nonabsorbable monofilament sutures resisted infection better than multifilament sutures or catgut. Absorbable synthetic PGA type of sutures also resisted infection better than plain or chromic catgut.

The ability of sutures to enhance infection is multifactorial. Bioadherence of the bacteria to the sutures is certainly one important factor (SDC-62). Monofilament polypropylene had less adherence than braided polyester sutures with or without coating with polybutylate by a factor of up to 10 times in one study (SDC-63). Nylon bound to fewer radiolabeled bacteria than several types of braided suture by a factor of 5 to 8-fold, and the degree of infection obtained in mice in the presence of different sutures correlated well (SDC-64). Different strains of bacteria also seemed to adhere to sutures with different affinities (SDC-65). Bacteria reaching the interstices of threads in a multifilament suture are protected from phagocytosis by leukocytes, as there is no significant leukocyte penetration into the multifilament sutures (SDC-66).

Several studies have now shown that a variety of suture materials can be impregnated with antibacterial substances and antibiotics including triclosan (SDC67–70), silver (SDC-71), gentamicin (SDC-72) and neomycin (SDC-73). All of these have shown the feasibility of reducing bacterial counts in wounds. A prospective randomized clinical trial (SDC-74) demonstrated that using antimicrobial sutures compared to standard sutures could reduce the infection rate in cerebrospinal shunt surgery from 21% to 4.3%. Another recent nonrandomized observational study involving 2088 operations compared the use of a PDS loop during a baseline period with a triclosan coated polyglactin 910 suture (Vicryl plus) during a subsequent time period. The wound infection rate was 10.8% in patients with abdominal wound closure with nonantibiotic sutures compared to 4.9% with the antibacterial sutures (SDC-75).

Wound closure techniques can also make a difference in the incidence of infection. Continuous fascial closure is clearly better than using interrupted sutures (SDC-76 to 78).

**Interpretation**

Braided sutures such as silk can cause as much as a 10,000-fold decrease in the numbers of bacteria necessary to cause an infection in humans. Monofilament sutures are much less prone to potentiating infections than multifilament sutures because of decreased bioadherence of the bacteria and improvement in the ability of phagocytic cells to reach bacteria on or within the sutures. Continuous sutures of the same material are associated with fewer infections than interrupted sutures, possibly because of reduction in tissue necrosis at suture sites associated with more even distribution of tension at the suture sites and also because less suture material is left in the wound. Impregnation of the suture materials with antimicrobials may be of some benefit, but it has not been tested sufficiently in well-controlled studies.

**TISSUE DAMAGE AND FOREIGN BODIES**

Because the elaboration of Halstedian principles a century ago, there has been little debate that excessive tissue injury and introduction of foreign materials increase the incidence of wound infections. The use of electrocautery for opening of wounds is used frequently although there is clear evidence that it may increase the incidence of infection (SDC-79-80). The expert consensus is that if electrocautery is to be used, it should be used primarily for pinpoint treatment of bleeders and not for all incisions. (An exception might be made in the presence of coagulopathy).

Techniques that involve obliteration of all potential dead spaces by multilayered closures are effective in preventing wound infections in contaminated areas (SDC-81-82).

**Interpretation**

Surgical technique is one of the primary factors in preventing wound infection. Poor surgical technique cannot be overridden by the use of antibiotics or any other method.

**DRAINS**

Drains are used frequently to remove excess fluid and blood from wounds or body spaces. For decades, it has been clear that drains should not exit through the working incision and that closed suction drainage is preferable to open drains in preventing infection.
In recent years, the potential benefit of even closed suction drains has been questioned and several meta-analyses involving thousands of patients have been done. In one analysis involving 36 studies with 5464 participants, there was no significant difference in the incidence of wound infection in orthopedic patients using a closed suction drain (SDC-83). Another report analyzing 664 patients with hip fractures showed no specific benefit of use of drains (SDC-94). There has also been no benefit of the use of closed suction drains in specific types of operations including colorectal surgery (SDC-85-86), uncomplicated liver resection (SDC-87), laparoscopic cholecystectomy (SDC-88), uncomplicated open cholecystectomy (SDC-89), abdominal surgery (SDC-90-91), gastric bypass surgery (SDC-92), incisional hernia repair (SDC-93-94), vascular surgery (SDC-95), thyroid procedures (SDC-96), median sternotomy (SDC-97), and tissue expander implant (SDC-98). Closed suction drainage may still be useful when production of large amounts of subcutaneous fluid is expected (such as abdominoplasty) or to detect leaks. Drains have been used effectively to instill local antibiotics at the end of operations with great success (8, SDC-99-100) (see prophylactic topical antibiotics).

Interpretation

The use of conduit drains and drainage through a working incision increases the incidence of infection. Closed suction drains may be useful for the removal of fluid from large potential dead spaces, but do not, themselves, prevent infection.

PROPHYLACTIC TOPICAL ANTIMICROBIALS

The use of alcohol (wine) to prevent infections in wounds was described by Hippocrates in the fourth and fifth century BC and later documented in biblical writings (Luke 10:33-34). The fact that any benefit was caused by an antimicrobial effect of alcohol was, of course, not known. It was not until Listerian times that other antimicrobial agents, such as carbolic acid, were discovered to have benefits in protecting against wound infection by killing bacteria in contaminated wounds. With the introduction of systemic antibiotics, it was quickly reasoned that these same antibiotics might be effective when applied topically in wounds. However, the first prospective randomized studies were not done until 1956 when it was shown that irrigation of the operative site with tetracycline reduced the incidence of SSI after appendectomy from 8.1 to 1.2% (SDC-101). By 1977, there were 11 randomized clinical trials and 6 retrospective studies, which supported the clinical effectiveness of topical antibiotics (SDC-102). Neomycin, ampicillin, and tetracycline were the drugs most commonly used. Several animal studies have shown that application of antibiotics into the incision will significantly reduce the incidence of infection to the same extent as systemic prophylaxis, but combined systemic and topical applications provided no additional benefit when the same antibiotics were used (SDC-103-105). In clinical studies, topical irrigation with an antibiotic is also more effective when the type of topical antibiotic is different from the systemic antibiotic being given, with evidence that they are additive (SDC-106-113). In a recent study in patients undergoing inguinal herniorrhaphy, topical gentamicin was equivalent to systemic gentamicin in preventing wound infections (SDC-114). In another study in which cefazolin was measured in both serum and wound drain fluid after intravenous or topical application, concentrations of cefazolin in the wound drain fluid were over 4,000 μg/mL, which remained high for 24 hours after topical application (SDC-115). When ampicillin was given beneath the fascia and into the subcutaneous space during wound closure, initial wound fluid concentrations exceeded 1000 μg/mL and were 73 μg/mL, and 14 μg/mL after 14 and 20 hours, respectively (SDC-116).

The timing of topical antibiotics is a crucial factor (SDC-117). There were no deep 30 day SSI when irrigation of the surgical site was performed by irrigation with a needle and a syringe containing kanamycin with or without cephalothin on an average of every 4.7 minutes throughout the operative procedures compared to 0.73% without antibiotic lavage.8 In a later randomized double blind study of GI and biliary procedures by the same group, 3% of patients with antibiotic irrigation developed infections compared to 9% in the control group (SDC-118). Use of a spray of a solution of cephalothin and gentamicin into the surgical site several times during cardiac surgery resulted in no deep SSI in 502 patients undergoing cardiopulmonary bypass.9 In another study, irrigations with penicillin in 368 clean general surgical procedures reduced the incidence of postoperative SSI from 3.5% to 0.27% (SDC-119). In a more recent study, kanamycin was infused into the subcutaneous wound space by means of a catheter, allowing it to dwell for 2 hours before extraction of the fluid by activating the closed suction device to which it was attached.10 Of 772 morbidly obese patients undergoing initial gastric bypass, there was only one primary deep SSI (0.13%) and two secondary deep infections (after spontaneous drainage of a seroma), totaling 0.39% for any deep infection.

With the demonstration that topical antibiotics could have a significant effect on the development of wound infections, there has been interest in developing techniques in which the antibiotics could be released over a longer period of time. Experimental studies have shown that the use of carriers such as poly(methylmethacrylate (SDC-120), polyglycolic acid (SDC-121); glyceryl monostearate (SDC-122), poly-(dl-lactide-co-glycolide) (SDC-123), glycerylmonostearate (SDC-124), and PMMA could be used as carriers for a variety of antibiotics including cefazolin (SDC-122-123), gentamicin (SDC-120, SDC-125), tobramycin (SDC-120), minocycline (SDC-121), and vancomycin (SDC-124). All of the animal models showed that the antibiotic-impregnated implants reduced bacterial counts in contaminated wounds and significantly protected against infections which were independent of and additive to systemic antibiotics (SDC-120-121, SDC-125). Significantly higher concentrations of the antibiotics were present at the location of the test sites. These or similar products have now been evaluated in a variety of clinical situations. An observational study in 1993 used tobramyacin-impregnated PMMA beads to successfully prevent infections in compound fractures (SDC-126-127). Gentamicin containing collagen sponges were placed randomly in 221 colorectal surgery patients, and this was associated with a significant reduction in the rate of infection of the wounds (18.4%-5.6%) (SDC-128). Collagen-gentamicin implanted sponges were evaluated for their effect in preventing sternal wound infections in a study of 2000 cardiac patients randomized to treatment and control arms (SDC-129). The incidence of wound infection was 4.5% in the treatment group and 9.0% in the control group (relative risk, RR = 0.47).

If topical antibiotics are effective in controlling wound infections, it seems reasonable that irrigation of the wound with other antimicrobials would also be effective. Several of these, such as povidone iodine solutions and chlorhexidine have been studied extensively but, in general, their uses have not been effective or have actually been deleterious (SDC-130-134).

As an extension of the use of topical antimicrobials to prevent infection, mupirocin (pseudomonic acid) has been shown to be as much as 97% effective in reducing nasal carriage of S. aureus (SDC-135). A recent analysis including the Cochrane Data Base cited 9 randomized clinical trials involving 3396 participants (SDC-136). When mupirocin was compared to either placebo or no treatment, there was a reduction of S. aureus infections associated with intranasal mupirocin (RR = 0.55). However, the infection rate caused
by other types of bacteria was significantly higher in patients treated with mupirocin (RR = 1.38).

**Interpretation**

Topical antibiotics are clearly effective in reducing wound infections and may be as effective as the use of systemic antibiotics. The combined use of systemic antibiotics and topical antibiotics may have additive effects, but this is lessened if the same antibiotic is used for both topical and systemic administration. Topical antibiotics work best if they are used throughout the procedure compared to simple irrigation of the wound at the time of closure. However, the most effective time interval for application has not been established. High concentrations of the antibiotic may be assured when it is injected into the wound and retained after closure or with the use of sustained release antibiotic containing materials which, when biodegradable, may not need removal. The use of such materials in clinical studies, however, has been very restricted. Using other antimicrobials such as povidone iodine solutions to decontaminate wounds has not been effective and has been shown to inhibit wound healing and/or increase wound infection. They should not be used.

**SYSTEMIC PROPHYLACTIC ANTIBIOTICS**

A recent “meta-analysis of meta-analyses” involving 250 clinical trials and 4809 patients has provided an estimation of the relative benefit of systematic prophylactic antibiotics to reduce infection for 23 different types of surgery. The type of antibiotic, timing, dosing, and type of procedure varied widely in this analysis, but the relative risk of developing infection for all types of operations with prophylactic systemic antibiotics versus no prophylactic antibiotics varied from 0.19 to 0.82, suggesting a generalized benefit regardless of the degree of contamination. Taken as a whole, the use of prophylactic systemic antibiotics decreased the incidence of wound infections by about one-half. This does not mean that prophylactic antibiotics should be used for every case, in as much as there are significant costs involved with their administration, they can have serious adverse effects and there is a risk of the development of antibiotic resistant pathogens or *Clostridium difficile* colitis. Because of this, there has been reluctance to use prophylactic antibiotics in clean cases. However, prospective randomized studies have shown a clear benefit in clean elective operations such as hernia and breast procedures (SDC-137-141). Recent reports have also shown significant protection against infections in patients with a cesarean section (SDC-142-143). A review of the use of antimicrobial prophylaxis in colorectal surgery, including 182 trials with 3880 participants and 50 different antibiotics, showed a definite benefit of prophylactic antibiotics compared to a placebo or no treatment (RR = 0.30). In that same study, combined therapy against both aerobic and anaerobic organisms and combined oral and intravenous antibiotic prophylaxis compared to intravenous alone had significant benefits (RR, 0.41 and 0.74, respectively).

**Timing of Administration**

In earlier studies, the administration of antibiotics before or at the time of operation in experimental animals with contaminated wounds would effectively prevent wound infections, but this benefit was lost after 12 hours (SDC-144–145). In a further refinement, there was a progressive loss of effectiveness of antibiotics within the first 3 hours after inoculation in a model where organisms were injected intracutaneously in guinea pigs (SDC-146). Subsequent clinical studies confirmed that preoperative administration of antibiotics were superior to postoperative administration (SDC-147-149). These studies initially defined the “golden period” with recommendations to administer prophylactic antibiotics in the first 2 hours before surgery. In subsequent clinical studies, the rates of surgical wound infection have been more clearly related to the time of administration with respect to surgical incision with a U-shaped curve for the length of time either before or after the time of incision (SDC-150). One study showed that the incidence of an SSI was least when cefuroxime (and metronidazole in colorectal cases) was administered 30 to 60 minutes before incision (SDC-151). Another recent study showed that the least infections occurred when the antibiotics were given 10 to 20 minutes before incision (SDC-152). The most effective time for antibiotics to be given was 1 to 30 minutes before the incision in 1922 patients undergoing elective total hip arthroplasty in 11 hospitals (SDC-153). In a large multicenter report involving 4472 patients in 29 hospitals, the timing of the administration of perioperative antibiotics was studied involving cardiac, hip-knee arthroplasty and hysterectomy cases. The best protection was seen when the antibiotic was given within the first 30 minutes before incision (SDC-Fig. 1 at http://links.lww.com/SLA/A121). Timing for vancomycin and other long-acting antibiotics is different. In a study of 2048 patients undergoing coronary artery bypass, the optimal time for administration of vancomycin was between 16 to 60 minutes (SDC-154). A further analysis of that study showed that when vancomycin was given at appropriate times, compared to inappropriate times, there was a savings of $4154/patient treated (SDC-155).

Despite the overwhelming evidence during the last 40 years, an analysis of 34,133 US Medicare patients undergoing cardiac, colo rectal, or orthopedic surgery and hysterectomy from January 1 to November 30, 2001, showed only 55.7% of the patients received their prophylactic antibiotic within 1 hour before incision (SDC-156). In a large National Surveillance Program in the United States, compliance with the administration of antibiotics within 60 minutes of surgery rose from 47.6% from the beginning of 2002 to 73.1% in the last quarter of 2005 (SDC-157). With better surveillance, the administration of antibiotics within the optimal time, at one hospital increased from 40% in 1985 to 99% in 1998 (SDC-158).

Numerous studies have now showed that a single dose of antibiotics for chemoprophylaxis is as effective as multiple doses in a variety of surgical procedures, including gynecologic surgery (SDC-159-160), colorectal surgery (SDC-161), surgery for closed long bone fractures (SCD-162) and a variety of other operations (SDC-163-166). Other studies have shown that prolonged administration of antibiotics for longer than 24 hours adds no benefit in neurosurgical procedures (SDC-167), thoracic surgery (SDC-168), colorectal cancer surgery (SDC-169), gastric and colorectal surgery (SDC-170), cardiovascular surgery (SDC-171) and penetrating abdominal trauma (SDC-172-173). Prolonged use of antibiotics not only increases the costs directly but also may be associated with an increased risk of acquired antibiotic resistance (SDC-171).

Not all studies, however, have shown that single-dose antibiotics are as effective as multiple dose antibiotics. One study compared one dose with three doses of cefmetazole in elective colorectal surgery (SDC-174). The single dose group had an incisional SSI of 14.2% compared to 4.3% in the 3-dose group (P = 0.009). A prospective randomized study of 838 adult patients undergoing elective coronary artery bypass grafting showed that 8.3% of patients receiving a single dose and 3.6% of patients with antibiotic administered more than 24 hours developed an infection (P = 0.004) (SDC-175). The reasons for these infections occurring at a higher incidence with single dose administration may well be related to ineffective concentrations in the blood occurring before the end of closure for a variety of reasons (SDC-176-178).

**Modifying Factors**

It is generally acknowledged that systemic antibiotics are effective only if they maintain therapeutic concentrations in the wound throughout the period of potential contamination. There are several factors, which can modify the concentrations of antibiotics in the
surgical wounds in addition to the ones already discussed. These include renal function, body weight, half-life of the antibiotic, use of cardiopulmonary bypass, use of transfusions for blood loss, aggressive fluid therapy, patient age, and rate of diffusion into the wound.

Renal Function
Most antibiotics are excreted by the kidney, some more rapidly than others. Therefore, renal function determines the half-life of serum concentrations to a major degree. Only a few antibiotics commonly used for prevention of infection are not affected by renal function including but not limited to clindamycin and metronidazole. Renal function is also decreased by the presence of hypotension, which will in turn increase half-life of renal-excreted drugs.

Weight
Obese patients require higher doses of antibiotics to achieve effective tissue levels. Morbidly obese patients given 2 rather than 1 gram of cefazolin preoperatively had higher tissue and serum concentration, which resulted in a reduction of wound infections from 16.5% to 5.6% (SDC-179). In another study, 230 patients with different degrees of obesity (BMI 40–49, BMI 50–59, BMI ≥ 60) were examined for blood concentrations of cefazolin after administration of 2 grams preoperatively (SDC-180). Blood and tissue levels were measured at the time of closure. Serum concentrations of the “resistance breakpoint” of 32 μg/ml or higher were obtained in 73%, 68%, and 52%, respectively. Therapeutic tissue levels at the time of closure were achieved in only 48.1%, 28.6%, and 10.0%, respectively from the lowest BMI to the highest BMI.

**Half-Life**

Drugs with a short half-life such as cefazolin do not have the ability to sustain therapeutic concentrations during long operations. In patients undergoing cardiopulmonary bypass, the prevalence of wound infections was lowest with prophylaxis with vancomycin compared to either cefazolin or cefamandol (SDC-181). Fluoroquinolones also have a prolonged half-life and could be useful for lengthy operations (SDC-182).

Selection of Drugs for Prophylaxis
In general, the antibiotic(s) used for prophylaxis must be effective against the expected pathogens. Typical drugs based on recommendations from a variety of sources (SDC-183-189) are shown in Table 1. Initial doses are shown in Table 2.

An important problem in selecting alternative agents for prophylaxis where there is possible allergy is the need, in all settings, for Gram-positive coverage for streptococci and methicillin-susceptible staphylococci. Untreated, these organisms have a high likelihood of causing infection due to a variety of virulence factors. If cephalosporins or penicillin derivatives cannot be used, clindamycin remains the best alternative. In addition, so called community acquired MRSA (CA-MRSA) are commonly susceptible to clindamycin, especially the USA300 strain that now predominates in the United States. This organism is replacing other strains of methicillin resistant staphylococci as the predominant pathogen in surgical site infections. Systemic aminoglycosides do not provide effective coverage for these organisms and quinolones have little activity against CA-MRSA. For this reason, where prophylaxis is needed for Gram-negative facultative and aerobic organisms, clindamycin should be added. In penicillin allergic patients undergoing procedures

<table>
<thead>
<tr>
<th>Surgical Service</th>
<th>Routine Pre-op Antibiotic</th>
<th>Penicillin or Cephalosporin Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Cefazolin Plus Vancomycin</td>
<td>Vancomycin OR Clindamycin Plus</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Cefuroxime</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Cefazolin Plus Metronidazole Or Ertapenem</td>
<td>Vancomycin OR Clindamycin</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>Cefazolin Plus or Minus Metronidazole</td>
<td>Gentamicin Plus Clindamycin</td>
</tr>
<tr>
<td>General Surgery/Endocrine</td>
<td>Cefazolin</td>
<td>Clindamycin Plus or Minus Ciprofloxacin</td>
</tr>
<tr>
<td>GU</td>
<td>Cefazolin</td>
<td>Clindamycin Plus or Minus Gentamicin</td>
</tr>
<tr>
<td>Hepatobiliary (complicated)</td>
<td>Cefazolin</td>
<td>Ciprofloxacin Plus or Minus Vancomycin</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Cefazolin Plus Vancomycin (craniotomy or implantation of a device)</td>
<td>Tobramycin Plus Vancomycin</td>
</tr>
<tr>
<td>Oncology</td>
<td>Cefazolin Plus Metronidazole (GI and pelvic cases only)</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Oral/Maxillofacial</td>
<td>Cefazolin</td>
<td>Clindamycin (clean surgeries) Gentamicin</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>Cefazolin Plus Vancomycin (Arthroplasties only)</td>
<td>Plus Clindamycin (GI and pelvic) OR</td>
</tr>
<tr>
<td>Orthopedic-Spine</td>
<td>Cefazolin</td>
<td>Vancomycin (clean surgeries) Ciprofloxacin (GI and pelvic)</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>Cefazolin</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Gynecology</td>
<td>Cefazolin</td>
<td>Vancomycin OR Clindamycin</td>
</tr>
<tr>
<td>Plastics, Reconstructive &amp; Hand Surgery</td>
<td>Cefazolin</td>
<td>Vancomycin OR Clindamycin (if allergic to Clindamycin)</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cefazolin Plus Vancomycin (synthetic graft only)</td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Cefazolin and cefuroxime may be interchanged. Some guidelines authorize ertapenem usage for colorectal prophylaxis.
where *Bacteroides fragilis* and other anaerobes must be covered (colorectal surgery, appendectomy), gentamicin or a quinolone is recommended with the addition of clindamycin. There has been a continuing increase in *Bacteroides fragilis* resistance to clindamycin but this agent seems to retain sufficient activity to continue on as an effective prophylactic agent. The difficulty in replacing *Clostridium* via a more active anaerobic agent, is the loss of activity against Gram-positive organisms.

The use of prophylactic vancomycin is becoming increasingly common, and we now recommend this for operative procedures in which prosthetic materials are placed. It is also recommended for patients undergoing median sternotomy or craniotomy. This is, however, a recommendation without a large body of data on effective dosing. Vancomycin has been used extensively as a therapeutic agent for MRSA. This drug has an unusual distribution and does not behave as a single compartment beta-lactams do. Steady state is not reached until the fourth dose on a q12 hourly dosing regimen. Therapeutic efficacy correlates most closely with a complex variable termed area under the curve. This is a variable determined by the height of the peak level and the trough level. In therapeutic settings, doses of 15 to 20 mg/kg (as actual body weight) given every 8 to 12 hour are recommended for most patients with normal renal function to achieve the suggested serum concentrations. In seriously ill patients, a loading dose of 25 to 30 mg/kg (based on actual body weight) can be used to facilitate rapid attainment of target trough serum vancomycin concentration.

Prophylactic therapy is based on having effective levels of the antimicrobial present throughout the operative period from skin incision to closure, and in some settings, one or two postoperative doses. It is not known, however, if dosing vancomycin at levels below 20 mg/kg will achieve these levels quickly. The primary problem is that dosing on an actual body weight basis will mean, for a 100 kg patient, 2 grams of vancomycin, infused at a maximal rate of 1 gm/hour. This will take 2 hours preoperatively, an excessive time that consumes substantial hospital resources. We, therefore, recommend beginning the infusion 1 hour before scheduled incision and continue the infusion intraoperatively until completed.

**Redosing**

Many operations extend past the half life of the commonly used antibiotics. Current recommendations for redosing interval are given in Table 3, based upon renal function.

**Interpretation**

The administration of systemic prophylactic perioperative antibiotics is among the most important of the currently available methods to prevent wound infection. Except for vancomycin and the fluquinolones, the most effective time for administration is within the first 30 minutes before the incision is made. The cephalosporins provide good early penetration into the wounds. Longer acting antibiotics like vancomycin and fluquinolones should be given between 1 and 2 hours before the incision. Redosing of antibiotics is important for short-acting antibiotics and should be given approximately 3 hours after the incision is made. Dosage should be adjusted for large body size. The combined evidence shows no benefit of administration of an antibiotic after the wound is closed in the vast majority of cases where there is not massive contamination. The practice of routine administration of 3 doses of antibiotics should be abandoned. Adjustments for redosing should be made for renal function and rate of drug elimination.

**IMPROVEMENT OF HOST DEFENSE INFLUENCE OF BODY TEMPERATURE**

Mild hypothermia in the range of 34 to 36 °C has a large number of adverse effects including increased blood loss and transfusion requirements (SDC-190), prolonged postanesthesia recovery (SDC-191), prolonged hospitalization (SDC-191-192), an increase in morbid myocardial events (SDC-192-194) and an increase in wound infections (SDC-195). Hypothermia is especially common in patients with trauma (SDC-196).

The effect of mild hypothermia on the development of wound infections has been studied particularly well in patients undergoing colorectal surgery. In one double-blinded study, 200 patients were randomly assigned to either a group which was managed with hypothermia or to a group managed with normothermia. Surgical wound infections occurred in 19% of the hypothermic patients compared to 6% of normothermic patients, and length of hospitalization was increased in hypothermic patients, further affecting cost. In another study involving patients with colon resection, hypothermia tripled the incidence of wound infection (SDC-193). Maintaining normothermia is also important in clean surgeries of short duration. Four hundred twenty-one patients having breast, varicose vein, or hernia surgeries were randomly assigned to a standard nonwarmed group or to two warmed groups, which had local and systemic warming (SDC-197). Nonwarmed patients had a 14% incidence of wound infection compared to 5% with warming. These findings were supported by another study of 290 surgical patients (SDC-198) where wound infections occurred in 11.5% of those with hypothermia compared to 2% with normothermia (relative risk 6.3). It has been reported that local warming with radiant heat was as good as systemic warming in preventing SSI (SDC-199). Numerous reasons for the adverse effects of hypothermia have been advanced. The most important of these is that hypothermia causes generalized vasoconstriction, which decreases subcutaneous blood flow and oxygen tension (14, SDC-195, SDC-200).

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**Table 2. Preoperative Dosing of Antibiotics**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Cefazolin</th>
<th>Cefuroxime</th>
<th>Ciprofloxacin</th>
<th>Clindamycin</th>
<th>Gentamicin</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤80 kg (≤176 lbs)</td>
<td>1 gram</td>
<td>1.5 grams</td>
<td>400 mg</td>
<td>600 mg</td>
<td>4 mg/kg</td>
<td>500 mg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>81–160 kg (177–352 lbs)</td>
<td>2 grams</td>
<td>3 grams</td>
<td>600 mg</td>
<td>900 mg</td>
<td>4 mg/kg</td>
<td>1000 mg</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>&gt;160 kg (&gt;352 lbs)</td>
<td>3 grams</td>
<td>3 grams</td>
<td>800 mg</td>
<td>1200 mg</td>
<td>540 mg</td>
<td>1500 mg</td>
<td>3000 mg</td>
</tr>
</tbody>
</table>

*Round to nearest 20 mg.
| Round to nearest 250 mg.*

**Table 3. Intraoperative Dosing Intervals (hours) for Selected Antibiotics Based on Renal Function**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>CrCl &gt; 50 mL/min</th>
<th>CrCl 20–50 mL/min</th>
<th>CrCl &lt; 20 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>3–4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>Ampicillin/sulbactam (Unasyn)</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5</td>
<td>Call Pharmacy</td>
<td>None</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>8</td>
<td>16</td>
<td>None</td>
</tr>
</tbody>
</table>

*Round to nearest 250 mg.*
Hypothermia also has adverse effects on antibody and cell-mediated immune defenses (SDC-193) and cytokine regulation (SDC-201). Several studies are emerging, which indicate that hypothermia may be even more beneficial than normothermia in preventing wound infections. In experimental animals, it has been shown that an increasing core temperature that occurs during bacterial infections is essential for optimal antimicrobial host defense (SDC-202). A recent study has shown that a number of critical immunological defense mechanisms are enhanced by hypothermia up to 40°C in humans (SDC-201).

**Interpretation**

Hypothermia increases the development of wound infection because of adverse effects on the physiologic and immunologic functions necessary to kill contaminating bacteria. Studies have not yet been done to show whether the effects of mild hypothermia/normothermia are additive or synergistic with the potential beneficial effects of hyperoxia, especially in either smokers or diabetic patients.

**EFFECT OF OXYGEN THERAPY**

Killing of ingested microbes by phagocytic cells, especially neutrophils, involves oxidative processes (SDC-203-205). Neutrophils rapidly lose their ability to kill bacteria below a tissue Po2 of about 20 to 40 mm Hg (SDC-204, SDC-206). As a consequence, reduction in the oxygen tension in wounds increases the incidence and severity of infections in humans (SDC-205-207). This is particularly important in surgical wounds (SDC-205) where oxygen tensions (Psq O2 10–55 mm Hg) are much lower than normal tissues (65 ± 7 mm Hg) and can reach near 0 mm Hg in infected wounds. In experimental animals, the incidence of wound infection is inversely related to tissue oxygen tension, and the effect is time-dependent, similar to the effectiveness of prophylactic antibiotics (SDC-208-210). The effects of oxygen and antibiotics are also additive. In one human study, an inverse correlation was observed between subcutaneous (Psq) O2 and the associated rate of postoperative wound infection. When the maximum Psq O2 concentrations were 40 to 49 mm Hg, 43% of the patients developed postoperative infection, but when the subcutaneous oxygen tensions were at least 90 mm Hg, no patients developed wound infection (SDC-Fig. 2 at http://links.lww.com/SLA/A122). Another study (SDC-211) showed there was a significant difference in tissue oxygen saturation at the operative site 12 hours after operation in patients who developed an SSI (Psq O2 = 43.4%) compared to those who did not (Psq O2 = 55.8%). Thus, tissue oxygen concentration is an excellent predictor of wound infection. Subcutaneous Po2 is considerably lower in laparoscopic surgery compared to open procedures (SDC-212), consistent with a surprisingly high incidence of wound infections after laparoscopy. Obese patients also have considerably lower Psq O2 with the same FiO2 compared to normal weight patients (SDC-213), perhaps contributing to the observed higher incidence of infections in obese patients.

These observational studies soon led to prospective randomized clinical trials comparing patients receiving 80% inspired oxygen versus those receiving 30% oxygen. In a well-controlled study of 500 patients with colorectal resections, 5.2% of the patients receiving 80% oxygen developed wound infections compared to 11.2% of patients receiving 30% oxygen. The mean intraoperative subcutaneous Po2 were 109 ± 43 and 59 ± 15 mm Hg, respectively, within each subgroup. In a double-blinded controlled trial of 300 patients undergoing elective colorectal surgery, patients were randomly assigned to receive either 80% or 30% FiO2 intraoperatively and for 6 hours after surgery (SDC-214). Surgical site infections occurred in 14.9% in those receiving 80% FiO2 compared to 24.4% of the patients receiving 30% FiO2 (RR = 0.46). Another study (SDC-215) compared complications in 2025 patients with surgeries expected to last 2 hours or more, randomized to receive inspired gas with 80% O2/20% nitrogen versus 30% O2/70% nitrous oxide. Patients with the higher FiO2 had fewer infections (7.7% versus 10%, RR = 0.72, P = 0.036). However, a role of nitrous oxide separate from the effect of FiO2 could not be excluded. Continuing positive airway pressure has been reported to increase oxygenation and reduce wound infection (RR = 0.27) in postoperative patients receiving 50% O2 (SDC-216).

In contrast to demonstrated effectiveness in these well-controlled studies, there have been 4 studies, which have failed to show reduction in postoperative infections with an increased FiO2. The first negative study (SDC-217) of 160 randomized patients, with a nonstandardized group of abdominal operations, compared FiO2 80% with FiO2 35%, but was underpowered and not homogenous with additional methodological problems. Importantly, more than 50% of these patients had laparoscopically assisted surgeries. The second study (SDC-218) had 143 patients undergoing Cesarean section but was stopped early. The third study (SDC-219) had 38 patients undergoing colectomy and showed a nonsignificant trend toward benefit but was underpowered. The fourth and most important of these studies enrolled 1400 patients undergoing laparotomy (SDC-220) and showed similar rates of overall infection. However, deep wound infections occurred in 2.9% of patients with 80% O2 versus 3.7% of patients with 30% O2, a reduction of 21.6%. More importantly, most patients received epidural anesthesia, which could increase subcutaneous blood flow. No significant adverse effects of 80% FiO2 have been observed in any of the studies.

Three meta-analyses using MEDLINE and Cochran databases have been published within the last 2 years (SDC-221-223), and all have shown a significant reduction of wound infection in patients receiving hyperoxia compared to those that did not (RR, 0.68–0.74), but these exclude the last negative study. The benefit was seen mostly in colorectal procedures but hyperoxia may be beneficial in other types of surgery as well. In a case-controlled study of spinal surgery, SSI occurred more frequently in patients receiving FiO2 less than 50% during the procedure (OR = 12 after controlling for other variables) (SDC-224).

**Interpretation**

There is little doubt that low subcutaneous concentrations of O2 at wound sites impairs the antibacterial functions of neutrophils and promotes the development of wound infections. Some studies show that increasing inspired O2 from 30% to 80% results in improved O2 tension at wound sites, increasing the ability to kill contaminating bacteria and decreasing the incidence and severity of wound infections. However, not all studies show a benefit, most likely because of other factors, which alter tissue Po2 that may alter the effectiveness of hypoxia, including body temperature, blood pressure, smoking, type of anesthesia, noncomparable patient populations, differing practice of fluid replacement, use of vasopressors, type of operation and tissue handling. Supplemental O2 should start with induction, but optimal concentration and duration of therapy have not been established. Current data would suggest it should be given for at least 2 hours after closure.

**GLUCOSE CONTROL**

It has been known for decades that surgical patients with diabetes have an increased incidence of major complications including poor wound healing, wound infections, cardiac compromise, and death (SDC-225-226). Infections have been particularly problematic in diabetic patients undergoing sternotomy for open heart surgery (SDC-225, SDC-227). In a report of 8910 patients, 18% of whom were diabetic, the incidence of deep sternal wound infections (DSWI) in diabetic patients was 1.7% compared to 0.4% for nondiabetics.
tive blood transfusion was an independent predictor of infection.17 were 13 studies (6 prospective) that demonstrated that periopera-
tion of tumor growth, and transmission of infections. By 1990, there
including reversal of shock and improved patient survival after acute
clinically significant hypoglycemia. Close monitoring is essential.
operation period resulted in a significant decrease in the incidence of
infections such as urinary tract infections or pneumonia. A
increase in wound infection and all but 2 reported an increase in other
infection such as age, length of operation, anesthesia risk, diabetes,
patients, having other conditions which are clearly associated with
reduction blood levels to less than 200 mg/dL in the immediate post-
decrease in wound infections after colorectal surgery (SDC-233) spinal surgery (SDC-234), pancreatic surgery (SDC-235), vascular surgery (SDC-236-237), and mastec-
tomy (SDC-238).
are there numerous adverse effects of hyperglycemia on the immune system (SDC-239). These include disturbances of mi-
crovascular responses, inhibition of complement function, increases in proinflammatory cytokine levels and some chemokines, inhibi-
tion of chemotaxis, impaired phagocytosis and intracellular killing (especially by PMNs) and disturbances in reactive oxygen species.
clotting, cytokines, growth hormones, and corticosteroids are all increased
by hyperglycemia, all inhibiting O$_2$ delivery to wounds.

Interpretation
Hyperglycemia is a risk factor for SSI independent from dia-
betes. High levels of glucose impair numerous host defense mecha-
nisms and the risk of SSI increases with increases of blood glucose.
However, with aggressive treatment with insulin, there is a risk of
clinically significant hypoglycemia. Close monitoring is essential. We recommend less than 180 mg/dL for a maximal glucose target.

TRANSFUSIONS AND FLUID MANAGEMENT

Although blood transfusions have obvious beneficial effects, including reversal of shock and improved patient survival after acute hemorrhage, they may also have significant adverse effects including an increased incidence of infection, pulmonary dysfunction, promo-
tion of tumor growth, and transmission of infections. By 1990, there
were 13 studies (6 prospective) that demonstrated that periopera-
tive blood transfusion was an independent predictor of infection.17 These studies included patients with abdominal surgery, open heart surgery, orthopedic surgery and burn injury. All of them showed an increase in wound infection and all but 2 reported an increase in other types of infections such as urinary tract infections or pneumonia. A dose/response was reported in 7 of the studies but was not recorded in 4.

A dose/response has also been reported in most of the subse-
quent publications. In a group of 548 patients undergoing abdominal
operations, septic complications occurred to a greater degree in pa-
tients receiving more than 3 units of blood (SDC-240). In 868 patients
with acute injuries, the corrected odds ratio for infection was 1.6 when 1
to 4 units were given but 6.4 when more than 4 units were given
(SDC-241). In 285 patients undergoing elective operations for gas-
trointestinal cancer, blood transfusion was an independent variable
when more than 1000 mL was transfused (OR = 6.5) (SDC-242). Both buffy-coat depleted packed red cells and white cell reduced (filter-
ted RBC) showed an increase in postoperative infections in a study of
697 patients with colorectal surgery, compared to no transfusion, with a corrected relative risk of 1.6 for 1 to 3 units of red cells and
3.6 for more than 3 units (SDC-243).

In a single center study involving 15,592 cardiovascular opera-
tions, blood transfusions were associated with an increased dose de-
pendent incidence of both wound and systemic infections (SDC-244).
A report from a large shock-trauma center studied the risk-adjusted
outcome in 1172 consecutive trauma patients with stratification for
the type of blood product.18 The risk of infection increased by 5% for
every unit of packed red blood cells.

There is some evidence that the incidence of infection increases
proportional to the length of storage of the blood. In one study of
colorectal rectal resections, blood stored for 21 or more days had an
overall infection rate, which was higher than blood stored for shorter
periods, 46% versus 32% (SDC-245). Another study showed that the
risk of pneumonia increased 1% per day with each day of storage of
the transfused blood (SDC-246). In an analysis of more than
6000 cases of cardiac surgery, blood stored 14 days or less was as-
associated with a 2.8% incidence of sepsis or septicemia compared to
4.0% with blood stored at least 15 days, but length of storage had no
effect on deep sternal wound infections (SDC-247).

There is considerable controversy concerning whether the non
red blood cell components of transfusion are associated with an
increased incidence of infection. Five hundred eighty-six patients
scheduled for elective colon surgery were randomized to leukocyte-
depleted or buffy coat poor blood. The patients with buffy coat poor
transfusions had a higher frequency of wound infection (12% vs 0%) (SDC-248). A recent meta-analysis of 12 randomized controlled trials
concluded that transfusion with buffy coat reduced red blood cells af-
after storage compared to WBC reduction before storage was associated
with an increase in infection (SDC-249). There is now good evidence
that there is a higher risk of death in association with WBC containing
alloageneic blood transfusions, especially after cardiac surgery.

Because allogeneic blood is associated with an increase in the
incidence of wound infections and overall infections, it has seemed
reasonable that the use of autologous blood donated before operation
would reduce infections. Indeed, this seemed to be true in one study of
385 patients undergoing elective orthopedic surgery where the
postoperative infection rate was 4.6% in patients receiving no trans-
fusion or autologous transfusions compared to 11.9% after allogeneic
transfusion (OR = 2.8) (SDC-250). In a follow-up study by the same
group, 6.9% of patients without transfusion, 1.2% of patients with
autologous transfusion and 12% of patients with WBC filtered RBCs
developed infections (SDC-251). In a study of resections for colo-
rectal cancers, transfusion of autologous blood was associated with
fewer postoperative infections (14%) than transfusion of homologous
blood (33%) (SDC-252). However, the use of autologous blood has
not been shown to reduce infections in other studies (SDC-253). Use
of a cell-saver has been advocated as a way to decrease the number of
alloageneic transfusions, but at least one study has shown that the rate
of infection was not decreased by using this technique (SDC-254).

The conclusions that transfusions increase the susceptibility to
microbial infections are not entirely without concern because these
observations have occurred primarily in patients with trauma or major
surgical procedures, and contributing factors cannot always be elimi-
nated in as much as transfusions are more often given to the sickest
patients, having other conditions which are clearly associated with
infection such as age, length of operation, anesthesia risk, diabetes,
and so on. Multivariable analyses have helped to reduce these concerns
and the fact that transfusions increase the susceptibility to infections
is now supported by several animal studies (SDC-255-259).
Fluid management during an operation could also have an effect on wound infections. It is now clear that restrictive fluid administration during many operative procedures may be beneficial compared to liberal administration of fluids, and this may be important in the development of wound infections in as much as Ringers’ solution as the sole means of fluid may reduce mean oxygen tension for 24 hours postoperatively by as much as 23% (SDC-260-261). In a prospective randomized study, fluid restriction decreased wound complications from 25% to 13% (SDC-262).

**Interpretation**

Virtually, all reports show an increased incidence of infection in transfused surgical patients, but some studies are difficult to interpret because of lack of comparability between transfused and nontransfused subjects. However, multifactorial analyses and animal studies show that there is a clear causal relationship between blood transfusion and the development of infections. The effect increases with the number of transfusions given, and there is some evidence that early leukocyte reduction by filtration will partially, but not completely, reduce the effect on wound infections. Blood transfusion is associated with alterations of a large number of immunologic mechanisms involving almost every segment of the immune response, the most important of which may be macrophage functions. As discussed before, anything that decreases the delivery of oxygen to a wound can increase the incidence and severity of infection. Administration of excessive amounts of crystalloids should also be avoided as this could possibly decrease tissue oxygen tension.

**SMOKING**

It has been known for decades that cigarette smoking is associated with adverse outcomes after surgery, including wound infection. This is particularly true with reconstructive and aesthetic procedures, but the association is clear with many other types of operations. One recent study of 84 patients undergoing aesthetic abdominoplasty reported the relative risk of smoking on development of infections was 12 (SDC-263). In 425 patients undergoing breast surgery for cancer, the odds ratio for developing infections in smokers versus nonsmokers was 2.95 for light smokers and 3.46 for heavy smokers with an even greater effect on the incidence of skin flap necrosis, OR 6.85 for light smokers and 9.22 for heavy smokers (SDC-264). Another study involving 84 patients showed an odds ratio for infection in smokers versus nonsmokers of 2.1 for major breast operations (SDC-265). Smoking was found to be the only modifiable risk factor for the development of infection (OR = 2.46) in a study of 1505 cases of ventral hernia repair in 13 Veterans Administration Hospitals (SDC-266). Also, in the Veterans Affairs National Surgical Quality Improvement database (NSQIP), involving 7543 patients in 14 medical centers primarily with vascular procedures, smoking was an important factor for the development of infections, particularly in obese patients (OR, 1.5–2.5) (SDC-267). The risk of reamputation was 2.5× higher after leg amputation in smokers than nonsmokers in one study (SDC-268). In 1000 patients undergoing elective cardiac surgery, sternal wound infections occurred with an odds ratio of 1.8 in patients who smoked (SDC-269). These findings were supported by a more recent study involving 7978 cardiac patients where the odds ratio for wound infection was 2.7 in patients who had a smoking history within the past year and 2.6 with a smoking history within the past 2 weeks. Surprisingly, the adjusted odds ratio for wound infection in smokers versus nonsmokers was 16.3 (3.6% vs 0.6%, P = 0.019) in a report of 489 patients undergoing ambulatory surgery (SDC-270). These clinical observations are strongly supported by a randomized clinical study involving 78 healthy volunteers in whom small standardized wounds were made on the buttocks and followed for the development of infection (SDC-271). Wound infections occurred in 12.6% of the wounds in individuals who smoked compared to only 2% in individuals who never smoked. Importantly, infections were significantly fewer in smokers who stopped compared to continued smokers after 4, 8, and 12 weeks of randomization (1.1% vs 21.7%). These studies all show that the risk of having wound infections in smokers compared to nonsmokers is at least doubled, depending upon the procedure, and is even higher involving procedures, which are associated skin flaps or obesity.

Although cessation of smoking seems to reverse the increased susceptibility to wound infections, the best length of time for abstinence still remains to be established. From the existing data, it would seem that cessation of 4 weeks might be sufficient (SDC-271-274).

One of the primary reasons for the adverse effects of smoking on surgical infections is that it clearly decreases oxygen delivery to the wound (SDC-275).

**Interpretation**

Smoking increases surgical wound infections via several well-established mechanisms including vasoconstriction, which is associated with decreased tissue Po2. Whether high inspired O2 and warming will decrease wound infections in smokers to levels of nonsmokers remains to be studied in prospective trials.

**DELAYED PRIMARY CLOSURE**

Delayed primary closure of contaminated wounds was utilized frequently during World War I, well before the discovery of antibiotics (SDC-276). Despite the benefit of this technique in war wounds, it was not used frequently in civilian practice (SDC-277) and not evaluated in controlled studies. In 1963, the first randomized study reported that primary closure of potentially contaminated abdominal wounds had a 42% incidence of infection whereas delayed primary closure was associated with only an 8% incidence (SDC-278). In an observational study, delayed primary wound closure was used in 146 patients matched to 146 similar patients undergoing standard wound closure during the same period (SDC-279). Wound infection was significantly lower in patients with delayed primary closure (2.1% vs 23.3%). In 1973, 300 highly contaminated cases had no invasive infections using delayed primary closure (SDC-280). The technique was felt to be particularly applicable to clean contaminated wounds in patients over the age of 60 or who had associated diabetes mellitus, malnutrition, or obesity (SDC-281). Not surprisingly, a strong indication for delayed primary closure was in wounds involving the intestine (SDC-282-283). The most recent (2009) prospectively randomized study of 81 patients with dirty abdominal incisions showed that SSIs developed in 42.5% of incisions closed primarily compared to 2.7% for delayed primary closure.50 In the same article, the authors reviewed 16 previously published studies comparing primary closure with delayed primary closure. A significant benefit was found in all studies except for those associated with appendicitis, typhoid ileal perforation, and ileostomy closure. Dirty abdominal wounds benefited the most. However, two meta-analyses concerning primary versus delayed primary closure showed no benefit for delayed primary closure in the treatment of appendicitis (SDC-284-285). There was also no advantage of delayed closure in patients with open fractures (SDC-286).

The benefit of delayed primary closure is related to improved blood flow at the wound edges, which develops increasingly over the first few days (SDC-287) and is associated with progressive increases in resistance to infections. In a classic experiment published in 1933 (SDC-288), a culture of S. aureus was applied at different intervals to surgical wounds in guinea pigs. When applied within 6 hours of closure, 100% of wounds became infected; when applied 24 hours after closure, 66% became infected; when applied 48 hours after closure, 56% became infected; 4 days after closure 10% were infected and...
5 to 7 days after closure, none became infected. More recent studies have shown that to cause an infection in a closed wound, it requires about a 10-fold increase in the size of bacterial inocula every day that passes up to 6 days (SDC-289). Still another study in guinea pigs confirmed the increasing resistance to infection of contaminated wounds over a 7 day period (SDC-290). Modications of the concept of delayed primary closure have recently gained some favor. As an example, closure of the wound in obese patients using wicks between the sutures in 384 morbibly obese patients was associated with an infection rate of only 0.78% (SDC-291). As another extension of this concept, negative pressure wound therapy has been used as a bridge to close contaminated wounds (SDC-292). Vacuum-assisted closure has also been used for the treatment of open abdominal wounds to assist in fascial closure (SDC-293–295) and in large open wounds because there are several advantages including the removal of exudate and acceleration of the development of granulation tissue.

Interpretation

The potential benefit of delayed primary closure in highly contaminated wounds is well established and is related to improved delivery of functional phagocytes to the wound site, increasingly through the first 5 to 6 days.

COMMENT

Using the principles and guidelines outlined in this review, it should be able to reduce wound infections in major clean operative procedures to less than 0.5%, in clean contaminated cases to less than 1.0% and in contaminated cases to less than 2.0%, even in high-risk patients. A checklist may be helpful to achieve compliance.

Checklist/Recommendations

1. The guidelines provided by the CDC and accrediting agents such as JACO have been followed. These include effective techniques for asepsis, air handling, cleaning of environmental surfaces, sterilization techniques, activities of surgical team members and surgical attire.

2. All members of the operative team have double gloved and changed gloves when any perforation is identified. Gowns and drapes have been used which prevent liquid penetration.

3. Preoperative showering with chlorhexidine within a few hours of the operation and the night before has been done and preoperative cleansing of the operative site with a chlorhexidine-impregnated cloth just before entering the operating room.

4. When hair removal is done, clippers have been used shortly before operation.

5. Reduction of skin organisms of both the surgical team and patient have been done using a combination of alcohol and chlorhexidine although other effective products including alcohol with iodophors are acceptable.

6. An antimicrobial incise drape has been used at operative sites where it is technically feasible to get good adherence to the skin.

7. Suture material has been selected which resists infection.

8. Dead spaces have been obliterated, where possible.

9. Minimal trauma to the wound itself by gentle handling of tissues and limited use of electrocautery has been accomplished and all devitalized tissue has been removed.

10. Conduit drains and drainage through a working incision have not been used.

11. Prophylactic topical antibiotics such as 0.1% kanamycin or another aminoglycoside (eg, gentamicin 160 mg/500 mL) solution have been used vigorously by pressure irrigation several times during an operation and before closure in all but the simplest cases to remove clots and devitalized tissues and to ensure high-tissue levels of antibiotic. In patients with a subcutaneous fat layer greater than 3 inches in depth, antibiotics have been infused into the wound after closure by means of a small catheter with removal of the fluid by closed suction drainage after dwelling for a few hours.

12. Prophylactic systemic antibiotics have been used according to guidelines in all surgical cases where the incidence of infections exceeds approximately 0.5% or when any foreign body is implanted.

13. Core temperature has been maintained at 36°C or higher throughout the perioperative period.

14. Inspired oxygen has been given at a sufficient concentration to maintain subcutaneous oxygen concentrations of approximately 100 mm Hg and pulse oxygen readings above 96.

15. All diabetic and hyperglycemic patients have received tight glucose control (blood glucose <180 mg/dL) during the perioperative period and for 2 to 3 days afterward in high-risk patients.

16. Transfusion of blood products has been limited.

17. Patients have stopped smoking for at least 4 weeks before operation for highly elective procedures, such as abdominoplasty.

REFERENCES


